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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	//

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,651	KORDYUM, ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 3/25/03 as Paper No. 10, in which claims were amended (claims 41, 49, 53, 58 and 63). Claims 41-64 are pending in the instant application.

Any rejection of record in the previous office action not addressed in this action is hereby withdrawn. This action is not final as there are new grounds of rejection made in this action that were not necessitated by applicants' amendment of the claims in Paper No. 10.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Each of the claims comprises the limitation of "cultivating the E. coli host cell under a culture condition that induces lytic growth of said cell without lysis". This phrase implies that it is the culture condition that results in lytic growth without lysis when it appears from the description of the invention provided by the instant application that the lytic growth without lysis is caused by the combination of mutations in the late genes of the lambda phage. The only culture condition shown to actually induce lytic growth is maintenance of a lambda cI857 ts

mutant at higher temperatures (>32°C). As written, the claim encompasses a large number of possible culture conditions that might contribute to "lytic growth without lysis" for lambda phage. There is no basis provided by the instant specification or prior art for envisioning such conditions other than temperature control for a cI857 ts mutant.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41, 49, 53, 58 are vague and indefinite in that the metes and bounds of the phrase "cultivating the E. coli host cell under a culture condition that induces lytic growth of said cell without lysis" are unclear on at least two grounds. First, the metes and bounds of "lytic growth without lysis" are unclear. Does this limitation mean that the cells are not lysed, or that lysis is merely delayed as compared to a control phage? Upon reading the specification, it appears that the limitation is intended to specify some sort of "delayed lysis" condition wherein the desired protein is expressed, the cell eventually lyses and the protein is released as a soluble, biologically active protein. Second, the phrase "a culture condition that induces lytic growth...without lysis" implies that it is the culture conditions that yield the delayed lysis phenotype. This is inaccurate. While the induction of lytic growth may be due to a change in culture conditions (e.g. increased temperatures for a lambda cI857 mutant), it is the combination of mutations present on the phage that appears to be responsible for the delayed lysis observed by applicants. It would be remedial

to amend the claim language to clearly indicate whether the phrase "lytic growth without lysis" means that the cells do not lyse, and to amend the claim to more clearly indicate that the change in culture conditions only induces lytic growth.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al (Molec. Gen. Genet., 1979, Vol. 175, pages 77-87; see the entire reference) in view of the 1997 Novagen catalog (pages 42-43).

Murray et al teach the construction and use of several lambda phages comprising mutations in genes affecting the phage mediated lysis (e.g. N, Q, S, and cI857) of the host for the purpose of increasing the expression of a desired heterologous gene carried by the phage (i.e.

polA) prior to host-cell lysis (e.g. the abstract). Murray et al teach that it was known in the art at the time of their experiments that the use of phage exhibiting delayed lysis of host cells to express a desired gene product from the phage chromosome results in many copies of the incorporated desired gene, as well as concomitant amplification of the gene product (page 77, column 2, 3d paragraph). Murray et al teach that their system can be practiced with direct lytic infection of an appropriate host cell or with induction of latently infected lambda lysogens comprising the mutations in late genes. Murray et al demonstrate expression of the polA gene product up to 200 fold over uninfected cells (page 86, first full paragraph). Murray et al teach that amplification of the polA product beyond what they have demonstrated utilizing their phage system may require fusion of the polA gene to another promoter either in lambda or in a multi-copy plasmid. The authors indicate that maintenance of polA on a multicopy plasmid is not reliable and would require the development of an effective method for limiting polA transcription by use of a metabolic repressor or inducer (page 86, column 2, first full paragraph). Thus, Murray et al suggest the use of "delayed lysis" phage to amplify the expression of the desired polA gene product from a plasmid DNA provided that a method of tightly regulating the expression of polA is developed.

Murray et al do not explicitly teach the temperature-induced lysis of a lambda lysogen to generate phage particles that are then used to lytically infect a second E. coli host cell that comprises a plasmid having a gene encoding a desired protein in order to produce the desired protein. Murray et al do not actually exemplify an embodiment wherein the phage of their invention was used to infect a host cell comprising a gene encoding the desired protein.

The 1997 Novagen catalog describe a T7 RNA polymerase-based system (pET) for the expression of desired proteins that provides high yields as well as providing tight control over basal levels of expression (e.g. see pages 42-43).

It would have been obvious to extend the teachings of Murray et al to include a copy of the heterologous gene encoding polA on a multicopy plasmid using a system such as the pET system described by the Novagen catalog because Murray et al teach it is possible to use a lambda cI857 comprising mutations in the late genes to delay lysis and increase desired protein yields and that it is desirable to further increase gene copy number by incorporating the gene in a multicopy plasmid that maintains tight basal levels of expression. The pET system is such a tight basal control system known in the art a the time of filing. One would have been motivated to alter the teachings of Murray et al to include the plasmid in order to receive the expected benefit, as taught by Murray et al, of increasing the amplification of polA expression. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using the pET system in the methods taught by Murray et al.

It would have been *prima facie* obvious for one of ordinary skill in the art to use a lambda cI857 lysogen to prepare a lysate comprising phage particles to use in infecting a host cell comprising a plasmid encoding the desired gene product because Murray et al teach that a lambda cI857 lysogen can be used in their invention and because phage stocks are and were routinely produced from such lysogens by the ordinarily skilled artisan. Such lysogens provide a stable, convenient source of phage which can be produced easily by "lysis from within" following induction of the lytic growth cycle. One would have been motivated to prepare phage from such a temperature sensitive lysogen in order to receive this benefit.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
June 16, 2003